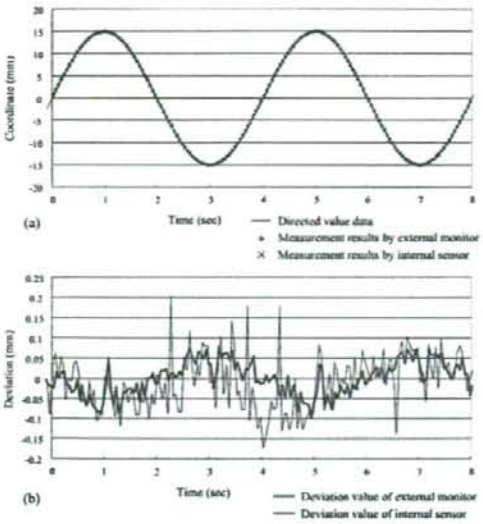

FIG. 4. The directed and the measured values in a sinusoidal motion. The result of each measurement with an external monitor and an internal sensor is shown. (a) Wave form of the directed and the values measured by both the external monitor and the internal sensor. (b) Deviations between the directed and the measured values.

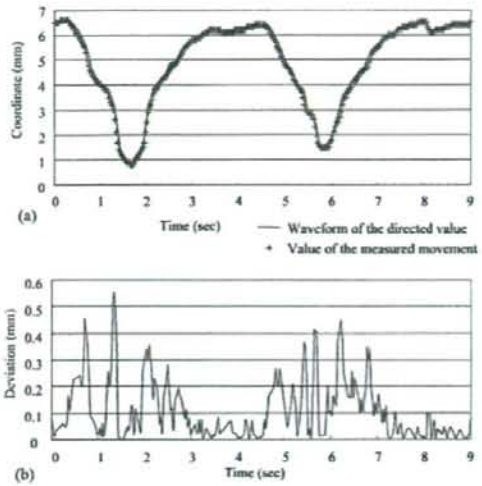

FIG. 5. Correlation of the directed value and the measured value on respiratory motion. (a) Comparison between the directed values and the output values measured by the internal sensor. (b) Deviations between the directed values and the measured value.

IV. DISCUSSION

High-precision radiotherapy as represented by stereotactic irradiation and IMRT has come to be widely applied today. These treatment methods can be much more sensitive to treatment-related errors such as setup errors and the errors occurred by internal organ motions than traditional methods with respect to the dose distribution of the targets and OARs.[14] Furthermore, in IMRT especially, the ones that use dynamic MLC techniques with moving leaves of a collimator during irradiation are particularly sensitive to organ motion due to the interplay between target and leaf motions.[15,16] Therefore, when high-precision radiotherapy is applied to an area that moves markedly due to respiration like the chest or upper abdomen, it is indispensable to confirm that the movement of the organ does not have a significant influence on the actually delivered dose distribution. Effects by motion, however, cannot be evaluated with currently available commercial-based RTP software and it is desirable to establish a means to simulate internal organ motion and estimate the influence of the motion when distributing dose in order to verify that the treatment plan meets the clinical criterion. Computer simulation seemed to be effective as a means; however, no computer program under the present situation can completely simulate the influence of treatment-related motions in the clinical field. We therefore believe that the verification by actual measurements was necessary. A moving phantom for dosimetry is necessary to measure this.

Though some movable phantoms have been reported so far,[8–10,17] these devices have not been able to simulate arbitrary movements of a body or an internal organ perfectly because the motion of the phantoms was generated from gyration by the motor and the reciprocal motion with the crank mechanism. Some other devices, which are able to achieve to reproduce arbitrary movement, have been reported, too.[11–13] One of these studies is about the device which drives a relatively small phantom made to evaluate the function of the CyberKnife® radiotherapy system, to deal with organ motion.[11] Another one has a similar mechanism to move a small radioactive marker for estimating the influence of or-

TABLE V. Positional accuracy on respiratory movement.

Axis	Directed amplitude (mm)	Measured amplitude (mm)	Deviation of amplitude (mm)	Maximum error of absolute accuracy (mm)	Maximum error of wave form reproducibility (mm)
X	4.4	4.4	0.0(SD=0.0)	0.48(SD=0.11)	0.16(SD=0.035)
Y	5.735	5.8	0.065(SD=0.0)	0.56(SD=0.12)	0.22(SD=0.039)
Z	4.388	4.3	0.088(SD=0.0)	0.51(SD=0.14)	0.16(SD=0.038)

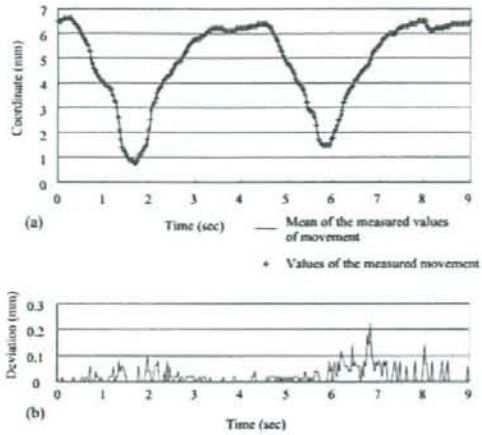

FIG. 6. The accuracy of positional reproducibility. (a) Comparison between the mean value of five histories of the value measured by the internal sensor and one history of the measurement. (b) Deviation of one history of the measurement from the mean value of five histories of the measurement.

gan motion to the PET or SPET by the same group.[12] These devices are able to achieve complex movement, however, there is no mention about the loadable weight of phantoms.[11,12] A device which can load a phantom for dosimetry has also been reported, however, the accuracy verification result by loading a heavy dosimetric phantom has not been mentioned.[13] Since the main purpose of our phantom system was to drive phantoms for the quality assurance of IMRT, it is mandatory to drive heavy dosimetric phantoms with high positional accuracy. We therefore developed the currently reported 3D movable phantom system that can simulate arbitrary movements with heavy dosimetric phantoms and verified the accuracy of the phantom system under the condition of driving them.

The characteristics of our newly designed 3D movable phantom system are as follows: the 3D movable phantom system must cover the 3D movement range and speed of motion of organs. We checked the articles on motions of the surface of the body, lungs, pancreas, liver, kidney, prostate, and seminal vesicle to confirm the adequacy of the function of the 3D movable phantom system, and the maximum range of movement of the organs was confirmed as 100 mm or less, except for one report in which the motion was 115 mm (average: 99 mm+SD 16 mm) of the diaphragm.[18,19] The confirmed maximum speed was 95.1 mm/s (average: 72.6 mm/s+SD 22 mm/s) concerning lung tumor motion.[20] We therefore selected the single-axis robot for this system with a movable range of 100 mm with a maximum table speed of 200 mm/s, and therefore, these mechanical specifications were sufficient to reproduce almost all treatment-related organ motions.

Since the main purpose of this system is to verify the influences of treatment-related uncertainties, one of the keys is the positional accuracy. With our system, the static positional errors of the system detected by the external monitor were less than 0.1 mm, and the internal sensor detected no detectable error. The positional accuracy in motion was also high enough to meet the requirements for radiotherapy because errors in the amplitude of motion were 0.088 mm or less (Tables IV and V). Though an error in the absolute accuracy of 0.56 mm was observed on respiratory motion, the error in reproducibility was 0.22 mm. Since reproducibility is most important for comparison, the trials are performed much in the same way as radiotherapy. In addition, the SD of the error in reproducibility was 0.039 mm, which is small, and the reproducibility in motion was high enough to satisfy the demand in radiotherapy. Furthermore, the SD of time was 0.0122 s for a respiratory cycle of 4.5 s and the SD of a sinusoidal cycle of 4 s, which were too small to be calculated. For the above reasons, we believe that the system has a sufficient accuracy to simulate the movement of internal organ and reproduce setup errors by routine procedures in radiotherapy.

As for the current limitations of this system, on the other hand, are as follows: The motion of internal organ cannot be fully simulated because this 3D movable phantom system moved the whole solid phantom as a representation of motion, however, the source-to-skin distance would be changed if motion factors in the ventrodorsal direction were included, while the system perfectly reproduces the movement in cases of simulating a patient's positional error, such as the setup error and the errors caused by intrafractional body movement. Such limitation of this system therefore has to be recognized when used to simulate internal organ motion to estimate the influence of the motion on the dose distribution. Organ motions due to respiration, however, are the largest organ motion and occur predominantly in the cranio-caudal direction. The movements in the ventrodorsal direction are fortunately small. We consider that even the effect of respiratory motion would be greatly assessable with our system, although it would be never be perfect. To solve this limitation, we are currently developing a new phantom system, which can independently simulate internal organ motions with movable components inserted into the solid body structure. This new phantom can be combined with this 3D movable phantom system to perform better simulation even if the issues in deformation would still remain. Another solution to bring the near complete simulation of treatment-related errors to realization would be a computer simulation.[16] The current program does not cover all factors that relate to the motions in the clinical field and that affect the dose distribution, like the scattered radiation by the MLC leaf edge, influence of a tongue and groove,[1] or 3D movement. Therefore, evaluation with phantoms would still be necessary, at least at present.

In addition to simulating the effects of treatment-related errors, this phantom system is very useful for some other purposes: to estimate the influences of motion on the shape of the CT images,[21] to empirically verify the efficacy of new treatment techniques dealing with the organ motion like gating[22–24] or tracking.[25,26] We have started to verify the

tracking capability of our newly designed image-guided radiotherapy system[26] with this phantom system.

V. CONCLUSIONS

We have developed a 3D movable phantom system, which allows us to simulate the impacts of treatment-related errors on dose distribution. The accuracy of the system in reproducing various motions was proved sufficiently high. This system also has a potential to evaluate the accuracy of a tumor-tracking radiotherapy system, which is expected to come into practical use in the foreseeable future.

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Current status of accelerated partial breast irradiation

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Abstract Accelerated partial breast irradiation (APBI) is a radiotherapy method used in breast-conserving therapy. In APBI, the tumor bed is topically irradiated over a short period after breast-conserving surgery. The fundamental concept underlying APBI is that more than 70% of ipsilateral breast tumor recurrence occurs in the neighborhood of the original tumor, and that hypofractionated radiotherapy can be applied safely when the irradiated volume is small enough. It is expected to reduce the time and cost required for conventional whole breast irradiation while maintaining equivalent local control. Several techniques including multicatheter interstitial brachytherapy, intracavitary brachytherapy, intraoperative radiation therapy, and 3D conformal external beam radiation therapy have been proposed, and each of them has its own advantages and drawbacks. Although APBI is increasingly used in the United States and Europe, and the short-term results are promising, its equivalence with whole breast radiation therapy is not fully established. In addition, because the average breast size in Japan is considerably smaller than in the West world, the application of APBI to Japanese patients is technically more challenging. At this point, APBI is still an investigational treatment in Japan, and the optimal method of radiation delivery as well as its long-term efficacy and safety should be clarified in clinical trials.

Keywords Breast cancer · Breast conserving therapy · Radiation therapy · Accelerated partial breast irradiation

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Abbreviations

APBI	Accelerated partial breast irradiation
BCT	Breast-conserving therapy
IBTR	Ipsilateral breast tumor recurrence
WBRT	Whole breast radiation therapy
BCS	Breast-conserving surgery
TR/MM	True recurrence/marginal miss
EF	Elsewhere failure
EIC	Extensive intraductal component
IORT	Intraoperative radiation therapy
EBRT	External beam radiation therapy
LDR	Low dose rate
HDR	High dose rate

Introduction

Several studies have reported that the survival rate after breast-conserving therapy (BCT) ia similar to that following mastectomy. Thus BCT has been established as a standard treatment for early breast cancer [1–6]. Concerning the role of radiotherapy in BCT, a meta-analysis of seven randomized controlled studies in which lumpectomy alone was compared with the combination of lumpectomy and radiotherapy showed that radiotherapy significantly reduced the incidence of ipsilateral breast tumor recurrence (IBTR) [6–13]. In the NIH consensus statement announced in 1990, the importance of radiotherapy in BCT was emphasized; whole breast radiation therapy (WBRT) at a total dose of 45–50 Gy, a dose of 1.8–2.0 Gy per fraction, and, if necessary, boost irradiation of the tumor bed were recommended.

The reported long-term IBTR rates after breast-conserving surgery (BCS) without radiation are between 10

and 40% depending on the extent of local resection and method of pathological evaluation, which in turn means more than half of the patients do not need radiation therapy. Therefore, some trials have been conducted to specify subgroups that do not require radiotherapy. In hormone receptor positive patients over 70 years of age, radiotherapy may be omitted with proper use of hormonal therapy because of relatively small benefit [14]. However, no other subgroup in which radiotherapy can be omitted has been specified [15]. In various treatment guidelines, it is recommended that WBRT should be performed in all patients after BCS.

According to a survey in Japan, radiotherapy is performed in approximately 70% of patients following BCS [16]. In the United States, the percentage is approximately 80% [17]; a relatively large number of patients do not undergo radiotherapy. This is possibly because radiotherapy requires a considerable expenditure and many hours.

The importance of systemic adjuvant therapy in breast cancer treatment has been increasing. Even in patients with early breast cancer for whom BCT is indicated, several months of chemotherapy is increasingly being given early after surgery, raising the issue of the order of chemotherapy and radiotherapy.

Thus, accelerated partial breast irradiation (APBI), in which the tumor bed is topically irradiated over a short period after BCS, was proposed.

Rationale of APBI

APBI was established based on the following rational background:

1. In more than 70% of patients with IBTR after breast-preserving therapy, recurrence is detected at the periphery of the primary tumor (true recurrence/marginal miss [TR/MM]) [18, 19]. The incidence of recurrence elsewhere (elsewhere failure [EF]) is similar to that of contralateral breast cancer; a "second cancer" may develop following treatment.
2. The treated volume is smaller than that of WBRT. Therefore, hypofractionated irradiation, in which the number of fractions is decreased by elevating the dose per fraction, may not cause significant late toxicities.
3. The radiation dose to the normal breast tissue other than the tumor bed is minimized, facilitating additional conservative therapy including radiotherapy, even when IBTR occurs in the future.
4. APBI can be completed within 1 week after surgery. Therefore, radiotherapy can be initially performed even in patients requiring chemotherapy; delayed radiotherapy dose not influence local control.

Indication for APBI

APBI is not indicated for all patients in whom BCT is selected. Previous studies have indicated that the IBTR rate after APBI was high in high-risk patients including those with large tumors, marked intraductal spreading or the presence of an extensive intraductal component (EIC), and young patients. Furthermore, this procedure has some limitations with respect to irradiation techniques; for external beam irradiation, the normal breast tissue including overlying skin, contralateral breast, heart, and lungs other than the tumor bed are exposed to an excessive dose of radiation. For brachytherapy, an excessive dose of radiation to overlying skin may be problematic.

Methods of APBI

APBI methods are mainly classified into three categories: brachytherapy, intraoperative radiation therapy (IORT), and external beam radiation therapy (EBRT). The following five techniques have been reported.

Brachytherapy

Topical irradiation is performed by placing a radioactive source in the tumor bed. Irradiation can be performed immediately after insertion, and takes 4 days to 1 week. The reproducibility of irradiation is favorable. However, the radiation dose in normal tissue, especially the overlying skin, is problematic. When inserting an applicator during surgery, irradiation can be started immediately following surgery. However, it is impossible to examine pathological margin status. Based on the type of applicator, brachytherapy is classified into two subcategories: multicatheter interstitial brachytherapy and intracavitary brachytherapy.

Multicatheter interstitial brachytherapy [20–25]

In the tumor bed, several guide tubes are placed in parallel at an equivalent interval on a single or several planes. Via these guide tubes, irradiation is performed using remote afterloading of ^{192}Ir. Initially, some studies employed a low dose rate (LDR) system [21]. However, recent studies have mainly selected a high dose rate (HDR) system [20, 23, 24]. Prescribed doses are approximately 50 Gy/5 days for LDR and 30–40 Gy/5 days (twice a day) for HDR. Guide tubes can be inserted during or after surgery. When inserting them during surgery, the lumpectomy cavity may be sutured. However, when inserting them following surgery, a removal cavity should be maintained to specify the tumor

bed from the outside. At the end of irradiation, guide tubes are percutaneously removed.

Intracavitary brachytherapy [26, 27]

Following surgery, a balloon-type applicator (Mammosite®) is inserted into a lumpectomy cavity under ultrasound-guidance. For irradiation, a radioactive source (^{192}Ir) is placed at the center of the balloon using the remote afterloading method. The removal cavity cannot be sutured. After balloon insertion/inflation, the distance from the skin cannot be maintained in some cases, or a space between the balloon and the removal cavity may affect dose distribution, making irradiation impossible; therefore, patients should be informed about such conditions prior to the procedure.

IORT [28, 29]

For IORT, the removal cavity is irradiated in the same room immediately after lumpectomy. Electron beam or low-energy X-ray is used. There are no limitations regarding the reproducibility of treatment or excessive radiation of the skin. However, it is impossible to examine pathological findings including the resection margin status prior to irradiation. In Japan, radiation shielding is another issue. Concerning electron beam application, the use of a self-shielding type device (Mobetron®) may minimize any necessary remodeling of an operating room. As a soft X-ray generator has low energy, it is not necessary to perform operating room remodeling.

IORT using electron beam [29]

Using a specially designed instrument for wound opening, an electron beam applicator is applied to the tumor bed, and anterior one-field electron beam irradiation is performed. Veronesi et al. performed single-dose irradiation at 21 Gy based on the results of a dose escalation study. Unnecessary radiation to underlying normal tissue can be avoided by mobilizing the mammary gland during surgery and placing a lead plate for shielding on its dorsal surface. As single-dose irradiation is completed during surgery, a removal cavity can be sutured.

IORT using soft X-ray [28]

Using a special soft X-ray generator with a bulbous applicator, the applicator is inserted into a removal cavity for irradiation before the cavity is sutured after lumpectomy. The dose gradient is steep. Vaidya et al. performed single-dose irradiation at 20 Gy in an area 2 mm distant from the stump and at 5 Gy in an area 1-cm distant from the stump. The device is smaller than an electron beam device (linear accelerator), and easy to manage.

EBRT (3D-conformal radiation therapy) [30–32]

Using the three-dimensional conformal technique, external beam irradiation is performed on the tumor bed. Radiotherapy treatment planning is performed based on CT images. However, to specify the target volume, the removal cavity should not be sutured, or when it is sutured, it must be marked with metal clips. There is enough time to review pathological findings. Various beam arrangements have been proposed [33, 34]. However, there are limitations such as the reproducibility of each fraction of irradiation and the radiation exposure of normal organs in the beam path. Recent studies with proton beams showed that the dose distribution was better than that for photon 3D-CRT or photon/electron 3-port irradiation [32, 35].

The features, merits, and limitations of each procedure are summarized in Table 1. There are differences in the timing of the pathological evaluation of the resected stump, work required for the procedure, and the reproducibility of treatment.

Table 1 Characteristics of modalities used in APBI

	Pathological confirmation before APBI	Work/ resource required for APBI	Conformity of APBI	Reproducibility of APBI
Interstitial (multicatheter)	Δ	Δ	Δ ~ ○	○
Intracavitary irradiation	Δ	○	Δ ~ ○	○
IORT (electron beam)	×	Δ ~ ×	○	○
IORT (soft X-ray)	×	Δ ~ ×	Δ ~ ○	○
3D-CRT	○	×	×	Δ

○ No problem; Δ some problem; × problematic

For IORT, it is impossible to accurately evaluate tumor pathology, especially the state of the resection margin, before irradiation. However, unnecessary irradiation in areas other than the target volume can be reduced. EBRT can be performed after obtaining pathological information. However, the inter-fractional reproducibility is lower than that of brachytherapy and IORT.

Results of APBI

The results of APBI previously reported are shown in Table 2. In some studies, local control was good, but not in others. In studies in which patients with large tumors, young patients, and those with an extensive intraductal component were regarded as eligible, the risk of local recurrence was high, suggesting the importance of patient selection in successful APBI.

Criticism of APBI

The rapid widespread use of APBI in clinical practice in the United States has contributed to advances in BCT. However, not all radiation oncologists agree with this strategy [36, 37]. The first goal of APBI is tumor control in the breast on the affected side. However, a consensus regarding the long-term results in comparison with WBRT has not been reached, although some studies have indicated that the short-term results obtained were similar to those of WBRT. APBI is effective at a 2 cm distance from the resected stump. Some researchers are skeptical about the difference between wider resection and APBI. In a randomized controlled trial of BCS, with or without WBRT, in which wider resection (quadrantectomy) was used as protocol treatment, the addition of WBRT still decreased the ipsilateral breast recurrence rate [38]. This suggests that WBRT is more advantageous than APBI.

In APBI, cancer recurrence in areas other than the periphery of the primary tumor bed is not considered. However, it is controversial whether such recurrence, which has been reported in a specific number of patients, may be ignored.

In addition, recent studies reported that WBRT improved the survival rate in patients undergoing BCT [39, 40]. The theoretical background of this benefit remains to be clarified. However, some investigators suggested that WBRT improves survival in a similar fashion to postmastectomy radiation therapy (PMRT); it improves tumor control not only in breast tissue but also in lower axilla, skin, and subcutaneous tissue in the radiation field, which prevents subsequent secondary dissemination [40]. It should be investigated whether APBI achieves ipsilateral breast control as well as all the benefits of WBRT in a large number of patients over a prolonged period.

NSABP B-39/RTOG 0413 trial

In 2005, a phase III NSABP B-39/RTOG 0413 collaborative comparative study was started to compare WBRT with APBI. According to an RTOG announcement, more than 150 patients per month were registered (as of May 2006). More than 70% of them underwent APBI by external irradiation. Initially a study of 3,000 patients was planned, but this was increased to 4,300. The eligibility criteria were disadvantageous for APBI in that young patients (18 years or older), those with T2 tumors (3 cm or less), those with EIC/DCIS, and those with lymph node metastasis (three or less positive nodes) were eligible, in whom the results of previous studies have suggested an increase in the local recurrence rate. If this clinical study shows that APBI is as effective as WBRT, APBI may become the main irradiation procedure after BCS.

Limitations of APBI in Japanese patients

The most important issues are breast size-related differences in the technique and the relationship between the removal cavity and the skin.

In Europe and the United States, a cavity after extirpation of the main tumor is maintained in many patients. However, in Japan, the cavity is sutured for cosmetic reasons. In this case, it is impossible to insert a device for intracavitary irradiation. For external irradiation, the target of irradiation can be visually confirmed when the margin of the removal cavity is marked with metal clips. However, the entire resected stump cannot always be accurately identified.

In Europe and America, the breast size is generally large, and lumpectomy, in which the extent of resection is about 1 cm from the gross tumor, is frequently performed. Therefore, the mammary gland tissue remains on the lateral, dermal, and pectoralis muscle sides of the removal cavity. In such cases, all-direction irradiation using a Mammosite® device is useful.

In Japan, the breasts are generally smaller, and wide excision involving a 2-cm free margin from the tumor is most commonly performed. In many cases, mammary gland tissue does not remain on the dermal or pectoralis muscle sides of the tumor. The target of irradiation is only the lateral stump. However, the dose distribution in the dorsoventral direction cannot be controlled with a Mammosite® device; therefore, an excessive dose of irradiation to the skin may be a treatment-limiting factor.

Recently, a new device (SAVI™, BioLucent, Inc., California, USA), in which multi-channel guide tubes at

Table 2 Results of APBI in Western countries

Series	*N*	Age	Size	Surgery	Margin status	EIC/DCIS allowed	Axillary LN
Guy's Hospital [21]	27	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Dissection in all pts.
Guy's Hospital [20]	50	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Level 3 dissection performed
NCI Budapest [24]	45	NR 38–78	<2 cm	Wide excision	Negative microscopically	Not allowed	Single nodal involvement allowed
WBH [25]	199	>40	<3 cm	Lumpectomy	≥2 mm 2 pts. 0–2 mm	Not allowed 21 pts. in-situ	12% 1–3 positive node
London Regional [23]	39	NR 39–84	<5 cm	Lumpectomy	Negative	Eligible	15% positive
Osaka Medical Center [22]	20	>20 32–72	<3 cm	Wide excision	1.5–2 cm macroscopically 3/20 positive in final pathology	Eligible	Level 1–2 dissection performed Positive in 3/20
WBH [26]	80	>40	≤3 cm	Local resection	≥2 mm	Eligible	≤3 positive nodes
NCI Milan [29]	101	NR 33–80	≤2.5 cm	Quadrantectomy	>1 cm macroscopically	No data	SNB or dissection in 96/101
Christie Hospital [30]	353	<70	≤4 cm	Tumorectomy	Incomplete excision accepted	Eligible	Clinically negative No dissection
NYU [31]	40	Post menopausal	<2 cm non-palpable	Lumpectomy	≥5 mm	Not allowed	No data
MGH [32]	20	NR 46–75	≤2 cm	Lumpectomy	≥2 mm	Not allowed	Pathologically negative

Series	RT Technique	RT dose	F/U	Local relapse	Survival	Toxicity	Good to excellent cosmesis
Guy's Hospital	LDR ^{192}Ir multicatheter	55 Gy/5–6 days	6 years	37% crude	70% actuarial read from figure	No data	83%
Guy's Hospital	MDR ^{137}Caesium	45 Gy/4 fr./4 days	6.3 years	18% crude	No data	No data	81%
NCI Budapest	HDR ^{192}Ir multicatheter	30.3–36.4 Gy/7 fr./4 days	81 mo. median	6.7% crude	93.3% actuarial cancer specific survival	Grade 3 fibrosis 2.2% Symptomatic fat necrosis 2.2%	84.4%
WBH	120 pts.: LDR 79 pts.: HDR	LDR: 50 Gy/4 days HDR: 32 Gy/ 8 fr./ or 34 Gy/10 fr.	65 mo. median	1% actuarial	87% actuarial OS	0%	99%
London Regional	HDR ^{192}Ir multicatheter	HDR: 37.2 Gy/ 10 fr./5–7 days	91 mo. median	16.2% actuarial at 5 years	86% actuarial OS	No data	Median subjective score 90/100
Osaka Medical Center	HDR ^{192}Ir multicatheter	HDR: 36–42 Gy/6–7fr./3–4 days	52 mo. median	5% crude	89% actuarial OS	Grade 3:5%	75%
WBH	Intracavitary (Mammosite)	34 Gy/10 fr./5 days	22.1 mo. median	2.9% 3 year actuarial	91.3% 3 year OS	No data	88% 3 year
NCI Milan	IORT (electron)	10–21 Gy Single dose 10–15 Gy with EBRT	42 mo. median	2% crude	98% crude	Grade1–2 22% Grade 3:1%	No data

Table 2 continued

Series	RT Technique	RT dose	F/U	Local relapse	Survival	Toxicity	Good to excellent cosmesis
Christie Hospital	EBRT (electron)	40–42.5 Gy/8 fr./10 days	8 years	25% actuarial	73% actuarial[a]	Marked telangiectasis 33% Marked fibrosis 14%	No data
NYU	EBRT (photon)	30 Gy/5 fr./10 days	12 mo.	0%	0%	No data	No data
MGH	EBRT (proton)	32 CGE/8 fr./4 days	12 mo.	0%	100%	Telangiectasia 3pts. Rib fracture 1 pt	100%

WBH William Beaumont hospital, *MGH* Massachusetts general hospital, *NYU* New York University, *NR* not restricted, *SNB* sentinel node biopsy, *LDR* low dose rate, *HDR* high dose rate, *CGE* cobalt gray equivalent, *F/U* follow-up, *OS* overall survival

[a] Read from survival curve

the circumferential region facilitate the fine control of dose distribution on the inner wall of the resected cavity, was developed. However, treatment results have not been published yet.

External irradiation also has a similar limitation. When irradiation is performed in the supine position, flat extension of the breast reduces the distance between the target of irradiation and the skin, leading to excessive radiation exposure of the skin.

For external irradiation, the conformity of dose distribution is less favorable than that for other procedures. As reported by Kosaka et al., the radiation dose administered to the normal mammary gland may be excessive when the resected cavity is relatively large compared with the breast.

When the breast size is large to some degree, these limitations may be overcome by suspending the breast in the prone position for irradiation. However, no study has investigated this issue in Japanese women.

Conclusion

Currently, we cannot recommend APBI as a standard option for BCT. However, in Europe and the United States, this procedure is being increasingly employed in clinical practice. If the results of clinical studies are good, it may accelerate this tendency. BCT in Japan markedly differs from that in Europe and the United States with respect to the surgical procedures and the average body habitus. In introducing APBI, unique strategies must be established and inspected.

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Feasibility of accelerated partial breast irradiation using three-dimensional conformal radiation therapy for Japanese women: a theoretical plan using six patients' CT data

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Abstract
Background Several methods have been reported for accelerated partial breast irradiation (APBI), but in Japan, there are few facilities where brachytherapy or intra-operative radiotherapy is available. Japanese women have smaller physiques than American women in general. Thus, we developed external beam plans for APBI using computed tomography (CT) data of Japanese patients, to investigate whether APBI using three-dimensional conformal radiation therapy is safely applicable for Japanese women, while verifying the dose distributions.
Methods We used CT data from six Japanese patients with early breast cancer, which were obtained in routine clinical practice during whole breast irradiation (WBI) after wide excision, and made 32 APBI plans according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and the Radiation Therapy Oncology Group (RTOG) 0413 protocol, which compared APBI with WBI. We then investigated the compliance to the dose constraints of the protocol.
Results None of 16 plans for the medial regions met the dose constraints regardless of laterality of the breast. The major reason was overdosage to the contralateral breast. Thirteen of 16 plans (81%) for the lateral regions met the dose constraints. The remaining three plans (19%) did not meet the dose limitation of the uninvolved normal breast, suggesting that a large ratio of the target to the breast was problematic.
Conclusions In Japanese women, patients with a laterally located small tumor can be candidates for APBI using three-dimensional conformal radiation therapy.

Keywords Breast cancer · Breast-conserving therapy · Accelerated partial breast irradiation (APBI) · Three-dimensional conformal radiation therapy

Abbreviations

APBI	Accelerated partial breast irradiation
WBI	Whole breast irradiation
NSABP	National Surgical Adjuvant Breast and Bowel Project
RTOG	Radiation Therapy Oncology Group
CT	Computed tomography
CTV	Clinical target volume
PTV	Planning target volume
DVH	Dose–volume histogram
IDL	Isodose line

Introduction

Breast-conserving therapy including breast-conserving surgery and subsequent radiation therapy is now the standard treatment for early-stage breast cancer. Moreover, many patients for whom the initial surgery would be mastectomy can undergo breast-conserving therapy following neoadjuvant chemotherapy [1, 2].

However, some patients choose to avoid whole breast irradiation (WBI) because of the long-term treatment of

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5–7 weeks, and some physicians either delay or omit WBI to start chemotherapy early. There are also other problems with late adverse effects of WBI including symptomatic radiation pneumonitis [3], ipsilateral arm edema [4] and breast edema or fibrosis with poor cosmesis [5].

Prospective randomized trials have shown that the majority of recurrences in the ipsilateral breasts of patients who did not receive WBI occurred in the vicinity of the tumor bed [6, 7]. It has also been shown that the recurrence rate in remote regions of the ipsilateral breast after breast-conserving therapy is similar to the incidence rate of contralateral breast cancer [6]. Consequently, clinical trials of accelerated partial breast irradiation (APBI), which is a method of irradiating the target volume around the tumor bed in a short period, were begun to investigate whether APBI can be an alternative to WBI. Several different techniques have been developed for APBI, including multicatheter interstitial brachytherapy [8, 9], the MammoSite™ balloon apparatus [10, 11], three-dimensional conformal external beam irradiation [12, 13], and intraoperative radiation therapy using low energy photons [14] or electrons [15]. The target volume for APBI is much smaller than that for WBI, so it is possible to increase the fraction dose to the target volume and shorten the treatment time to less than 1 week while decreasing the dose to the surrounding normal tissues regardless of the technique.

Both adverse events and local control rates have been reported to be satisfactory in early trials [16, 17]; therefore, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) began a randomized phase III trial comparing APBI to conventional WBI for women with Stage 0, I, or II breast cancer (NSABP B-39/RTOG 0413) [18].

In Japan, the demand for APBI is expected to increase. Nose et al. [19] presented the first report on APBI with high-dose-rate interstitial brachytherapy applied to Japanese women in 2006. However, there are few facilities where brachytherapy or intra-operative radiotherapy is available. Thus, we developed external beam APBI plans using computed tomography (CT) data from Japanese patients, obtained during routine WBI clinical practice at Kyoto University Hospital, and investigated whether APBI using three-dimensional conformal radiation therapy is safely applicable for Japanese women, while verifying that the dose distributions meet the dose constraints of the NSABP B-39/RTOG 0413 protocol.

Materials and methods

We used CT data from six Japanese women with early breast cancer, which were obtained for WBI after breast-conserving surgery at Kyoto University Hospital, and made three-dimensional conformal external beam plans. For every patient, we made virtual plans for the other three quadrants as well as for the true primary quadrant in the following way. Additionally, we made four virtual plans for the contralateral breast for two patients. So we made 32 plans in total (16 plans for each side).

We regarded the excision cavity as the target volume according to the NSABP B-39/RTOG 0413 protocol [18]. If the excision cavity cannot be identified on computed tomography, we assumed the excision cavity to include all clips, which were placed to mark the resection margin during the breast-conserving surgery. For contouring in quadrants other than the original, we assumed a virtual excision cavity of approximately the same size near the center of the quadrant. We then added the prescribed margin to the aforesaid excision cavity to define the clinical target volume (CTV) and planning target volume (PTV), and to define the structure "PTV_EVAL", which is only used for dosimetric analysis. According to the protocol, the details of the contouring target volumes are as follows.

CTV

CTV is defined by uniformly expanding the excision cavity volume by 15 mm, but limited to 5 mm from the skin surface and by the posterior breast tissue extent (pectoralis muscles are not to be included).

PTV

PTV is defined by uniformly expanding the CTV by 10 mm.

PTV_EVAL

PTV_EVAL is defined by limiting the PTV to 5 mm from the skin surface and by the posterior breast tissue extent.

For planning, we also conformed to the NSABP B-39/RTOG 0413 protocol. In simplest terms, the beam arrangements included non-coplanar 3-, 4-, and 5-field beams using 6-MV photons. The 4-field technique consists of left anterior superior-to-inferior oblique, left anterior inferior-to-superior oblique, right anterior inferior-to-superior oblique, and right posterior superior-to-inferior oblique for a right breast lesion (Fig. 1). We did not use the 3-, or 5-field technique for simplicity and to compare the plans. We did not use intensity-modulated radiotherapy because not all facilities can use this. For complete information on contouring and beam arrangement, refer to the NSABP B-39/RTOG 0413 protocol.

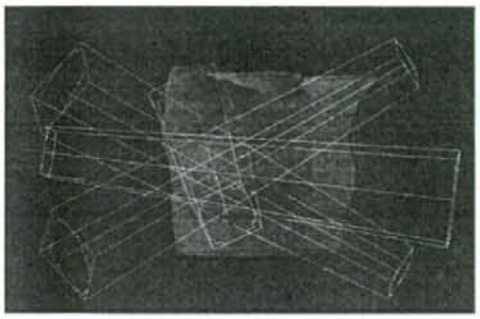

Fig. 1 Four-field beam arrangement of three-dimensional conformal beam radiotherapy

The dose was prescribed to the isocenter of the treatment fields and a total of 38.5 Gy was assumed to be given in 10 fractions in 5 days. In all plans we calculated a dose–volume histogram (DVH) and investigated the compliance with dose constraints described in the NSABP B-39/RTOG 0413 protocol. Dose constraints are listed in Table 1.

We did not evaluate the DVH of the thyroid because some computed tomography did not include the thyroid structure in the imaging area.

After we investigated the compliance with dose constraints, we determined why the plans did not comply with dose constraints.

Results

The mean and median sizes of the excision cavity, including the virtual cavity, were 19 and 16 cc, respectively (range 6–72 cc) (Table 2). The mean and median sizes of the CTV were 85 and 71 cc, respectively (range 43–232 cc). The mean and median sizes of the PTV_EVAL were 139 and 113 cc, respectively (range 77–370 cc). The mean and median sizes of the uninvolved normal breast were 486 and 426 cc, respectively (range 326–1087 cc). The mean and median ratios of the PTV_EVAL to the uninvolved normal breast were both 0.30 (range 0.16–0.50).

The mean and median coverage of the CTV by the 100% isodose line (IDL) were 40 and 43%, respectively (Table 3). The mean and median coverage of the CTV by 95% IDL were both 91%. The mean and median coverage of the PTV_EVAL by 100% IDL were 37 and 39%, respectively. The mean and median coverage of the PTV_EVAL by 95% IDL were 86 and 85%, respectively.

Thirteen of 32 plans (41%) met all dose constraints described in the NSABP B-39/RTOG 0413 protocol, whereas the other 19 plans (59%) did not. Categorized by medial and lateral quadrants, the details of the dose constraints of the unsuccessful plans are shown in Table 4.

None of the 16 plans for the medial quadrants met the dose constraints regardless of the laterality of the breast. The major reason was overdosage to the contralateral breast (14 plans). Overdosage to the ipsilateral lung was seen in four plans in right-sided lesions and in five plans in left-sided lesions. Overdosage to the heart was seen in four plans in right-sided lesions and in six plans in left-sided lesions, and overdosage to the uninvolved normal breast was seen in four plans only in left-sided lesions.

For the lateral quadrants, 13 of 16 plans (81%) met the dose constraints. The remaining three plans (19%) did not meet the dose constraint of the uninvolved normal breast. No overdosage to the contralateral breast, ipsilateral lung or heart was seen.

An example of a plan which met the dose constraints is shown in Fig. 2a. The WBI plan for the same breast is also shown for comparison (Fig. 2b). Additionally, DVHs of the ipsilateral lung and the heart in both plans are shown in Fig. 2c, d. Note that the fraction dose and the total dose are different between the two plans, however, we can decrease the ipsilateral lung dose and the heart dose in the APBI plan.

Discussion

For WBI there are problems regarding the time needed for treatment, sequencing with chemotherapy and adverse

Table 1 Dose constraints described in NSABP B-39/RTOG 0413 protocol

Uninvolved normal breast	Ideally, <60% of the whole breast volume should receive ≥50% of the prescribed dose and <35% of the whole breast volume should receive the prescribed dose
Contralateral breast	The contralateral breast volume should receive <3% of the prescribed dose to any point
Ipsilateral lung	<15% of the lung can receive 30% of the prescribed dose
Heart (right-sided lesions)	<5% of the heart should receive 5% of the prescribed dose
Heart (left-sided lesions)	The volume of the heart receiving 5% of the prescribed dose should be less than 40%
Thyroid	Maximum point dose of 3% of the prescribed dose

effects. APBI is expected to be an alternative to solve these problems.

Among APBI techniques three-dimensional conformal external beam irradiation is a non-invasive technique and can be done with sufficient pathologic information including the margin of resection, although it is affected by setup errors and respiratory movement and the dose to the surrounding normal tissues is higher than in other methods.

In the US many early trials have been investigated. It has been reported that acute adverse effects are tolerable and the ipsilateral breast control rate and cosmetic outcomes are satisfactory in all methods [16, 17].

As in the US, in Japan, the demand for APBI will likely increase in the near future, but there will be many problems other than efficacy when APBI is introduced into Japan. First, there are very few facilities where brachytherapy or intra-operative radiotherapy is possible compared to the number of patients who undergo breast-conserving therapy. External beam irradiation, however, can be done in almost all facilities where radiation therapy is available. Second, there is difference of physique, including the shape and size of breasts between Japanese and American women. Generally speaking, Japanese women have smaller breasts than American women; thus the ratio of breast cancer to breast is different when the size of the breast cancer is the same. So it is uncertain whether we can decrease the dose to the surrounding normal breast.

As a result of our feasibility study of APBI for Japanese women, the median size of the excision cavity was 16 cc, which was almost equivalent to the results of American reports (12–24 cc) [12, 13, 20]. The median size of the PTV_EVAL was 113 cc, which was smaller than the results of American reports (155–240 cc) as was the median size of the CTV (71 vs 112 cc), although these American reports included cases of smaller CTV or PTV margin compared to the NSABP B-39/RTOG 0413 protocol. The smaller size of the PTV_EVAL in our result was due to the small breasts of Japanese women, which excluded many volumes of PTV_EVAL outside the ipsilateral breast and the first 5 mm of tissue under the skin. The median ratio of the PTV_EVAL to the uninvolved normal breast was 0.30. This was larger than in American reports (0.17–0.23). These findings suggest that the

Table 2 Sizes: excision cavity, CTV, PTV_EVAL, and uninvolved normal breast

Structure	Mean	Median	Range
Excision cavity	19 cc	16 cc	6–72 cc
CTV	85 cc	71 cc	43–232 cc
PTV_EVAL	139 cc	113 cc	77–370 cc
Uninvolved normal breast	486 cc	426 cc	326–1,087 cc
PTV_EVAL/uninvolved normal breast	0.30	0.30	0.16–0.50

CTV clinical target volume, *PTV* planning target volume

PTV_EVAL is defined for dosimetric analysis

Table 3 Dosimetric findings: CTV, PTV_EVAL, and uninvolved normal breast

Dosimetric characteristics	Mean (%)	Median (%)	Range (%)
Maximum dose (% of prescribed dose)	106	105	101–114
CTV coverage			
100% IDL	40	43	1–72
95% IDL	91	91	80–100
PTV_EVAL coverage			
100% IDL	37	39	1–70
95% IDL	86	85	70–99
Uninvolved normal breast			
100% IDL	13	12	2–31
50% IDL	57	56	42–79

CTV clinical target volume, *PTV* planning target volume, *IDL* isodose line

PTV_EVAL is defined for dosimetric analysis

Table 4 Compliance with dose constraints

Quadrant	Side	Number of plans	Number of successful plans	Reasons for unsuccessful plans	
				Overdosage to	
Medial	Right	8	0	Contralateral breast	7 plans
				Ipsilateral lung	4
				Heart	4
	Left	8	0	Contralateral breast	7
				Uninvolved normal breast	4
				Ipsilateral lung	5
				Heart	6
Lateral	Right	8	7	Uninvolved normal breast	1
	Left	8	6	Uninvolved normal breast	2

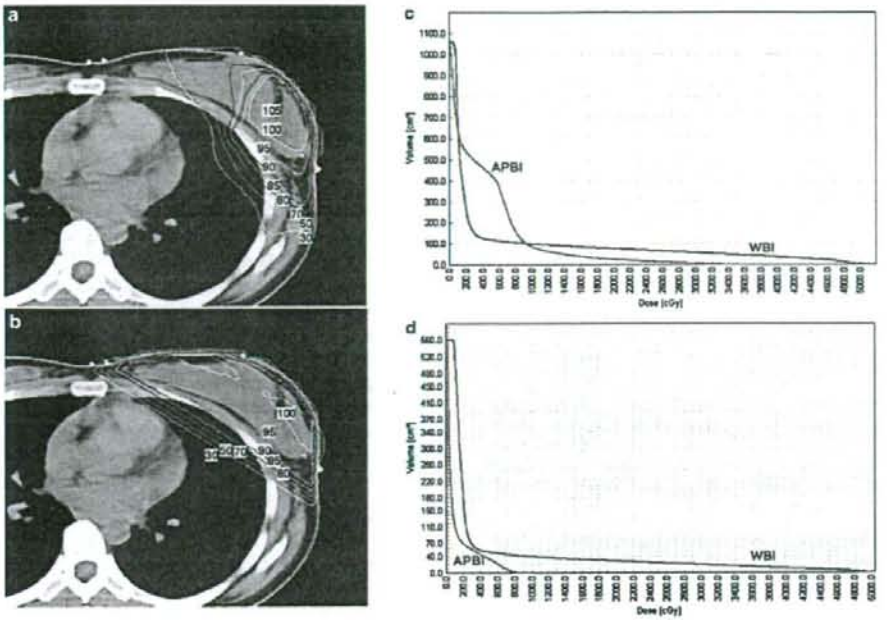

Fig. 2 Comparison of dose distribution between APBI **a** and WBI **b**. *Lines* are isodose lines and *digits* are percentage of the prescribed dose (APBI: 38.5 Gy, WBI: 50 Gy). **c** is a dose-volume histogram (DVH) of the ipsilateral lung in both plans, and **d** is the DVH of the heart. After considering the difference of the prescribed dose between two plans, the irradiation dose of the surrounding normal tissue is lower in the APBI plan, as is the irradiated volume

Japanese women in our study had smaller breasts than American women (the breast sizes of the American women were not clear).

The coverage of the PTV_EVAL by 95% IDL was lower than those in American reports (85 vs 100%) [13]. This was due to the larger ratio of PTV_EVAL to the uninvolved normal breast.

For the medial quadrants, no plans complying with dose constraints can be made. In the beam arrangement to the medial quadrants, the medial beam usually crossed the center line, which resulted in overdosage to the contralateral breast, and if the medial beam is steeper to avoid overdosage of the contralateral breast, it often causes overdosage to the ipsilateral lung or the heart. Consequently, plans for the medial quadrants are difficult regardless of the laterality of the breast if we comply strictly with the dose constraints of the protocol.

For the lateral quadrants, 13 of 16 plans (81%) met the dose constraints, but the remaining three plans (19%) did not meet the dose limitation of the uninvolved normal breast. It appears that the dosage of the uninvolved normal breast correlates with the ratio of the target to the uninvolved normal breast (Fig. 3); thus, it is difficult for patients with large primary tumor, a small build or small breasts (the ratio of the PTV_EVAL to the uninvolved normal breast is >0.3) to meet the dose constraints. Although the breast cancer had to be less than 3 cm to be eligible for the NSABP B-39/RTOG 0413 protocol, we need to have more strict criteria for the size of the tumor in women with a small build.

Recently, a new beam arrangement using a combination of photons and electrons was proposed by Massachusetts General Hospital [20]. This beam arrangement seems to be more suited to Japanese women than that of the NSABP B-39/RTOG 0413 protocol. With this technique, more cases are expected to comply with the dose constraints, and we will investigate whether this technique is feasible for Japanese women. Furthermore, we need more consideration of CTV, which is a region regarded to be at risk for microscopic tumor extension. In the NSABP B-39/RTOG 0413 protocol, the CTV margin around the excision cavity is 15 mm, but Vicini et al. [21] showed that a margin of 10 mm is adequate in >90% of patients treated with PBI. Additionally, taking into account differences in the extent

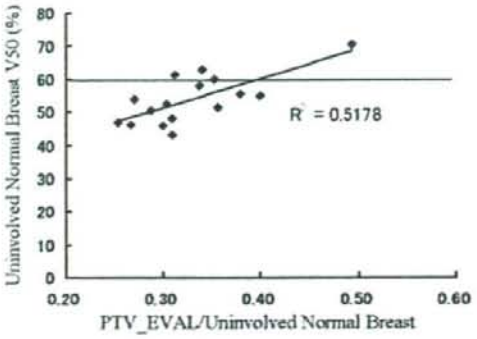

Fig. 3 Correlation between the dosage of the uninvolved normal breast and the ratio of PTV_EVAL to the uninvolved normal breast in APBI plans for lateral regions. Dose constraint of the uninvolved normal breast is lined (<60% of the whole breast volume should receive ≥50% of the prescribed dose). The higher ratio probably leads to non-compliance with the dose constraint. In other words, patients with a laterally located small tumor can be good candidates for APBI

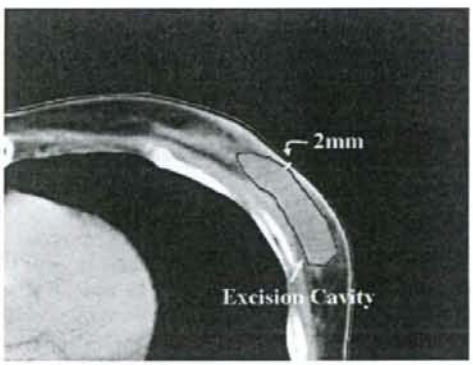

Fig. 4 Some patients have a mammary gland or excision cavity in the first 5 mm of tissue under the skin. For these patients we may need to expand CTV to include the mammary gland or the excision cavity

of surgery between the US and Japan, we may be able to set the CTV margin smaller than that of the NSABP B-39/RTOG 0413 protocol.

There is another problem with CTV. The first 5 mm of tissue under the skin is excluded from CTV in the protocol, probably because a hypothesis exists that there is no mammary gland in this region. For some Japanese patients this CTV is insufficient because it appears on CT that they have a mammary gland or excision cavity in this region (Fig. 4). We may need to expand CTV for them, but this increases the dose to the skin so adverse effects may be worse. We must define CTV for the treatment of Japanese women instead of using the CTV in the NSABP B-39/RTOG 0413 protocol.

In this context, there is the problem of "the excision cavity". In most cases, the excision cavity cannot be identified because many Japanese surgeons close the excisional cavity to maintain good cosmesis. This causes difficulty with the contouring target volume. Therefore, when we perform APBI, we must ask surgeons to show the stumps clearly, for example, clipping the excision margin or changing their surgical techniques if necessary.

In conclusion, in Japanese women, patients with a laterally located small tumor can be candidates for APBI using three-dimensional conformal radiation therapy at this time, although patients with a medially located tumor can not. We must consider the dose constraints or the CTV margin, and must try other beam arrangements such as a combination of photons and electrons so that more patients can be candidates for APBI with external beam irradiation.

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IL12RB2 and *ABCA1* Genes Are Associated with Susceptibility to Radiation Dermatitis

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Abstract

Purpose: Severe acute radiation dermatitis is observed in approximately 5% to 10% of patients who receive whole-breast radiotherapy. Several factors, including treatment-related and patient-oriented factors, are involved in susceptibility to severe dermatitis. Genetic factors are also thought to be related to a patient's susceptibility to severe dermatitis. To elucidate genetic polymorphisms associated with a susceptibility to radiation-induced dermatitis, a large-scale single-nucleotide polymorphism (SNP) analysis using DNA samples from 156 patients with breast cancer was conducted.

Experimental Design: Patients were selected from more than 3,000 female patients with early breast cancer who received radiotherapy after undergoing breast-conserving surgery. The dermatitis group was defined as patients who developed dermatitis at a National Cancer Institute Common Toxicity Criteria grade of ≥2. For the SNP analysis, DNA samples from each patient were subjected to the genotyping of 3,144 SNPs covering 494 genes.

Results: SNPs that mapped to two genes, *ABCA1* and *IL12RB2*, were associated with radiation-induced dermatitis. In the *ABCA1* gene, one of these SNPs was a nonsynonymous coding SNP causing R219K ($P = 0.0065$). As for the *IL12RB2* gene, the strongest association was observed at SNP-K (rs3790568; $P = 0.0013$). Using polymorphisms of both genes, the probability of severe dermatitis was estimated for each combination of genotypes. These analyses showed that individuals carrying a combination of genotypes accounting for 14.7% of the Japanese population have the highest probability of developing radiation-induced dermatitis.

Conclusion: Our results shed light on the mechanisms responsible for radiation-induced dermatitis. These results may also contribute to the individualization of radiotherapy.

Breast-conserving therapy, consisting of breast-conserving surgery and prophylactic breast irradiation, is the standard therapy for patients with early breast cancer. In most institutions, a total dose of 45 to 50 Gy is delivered to the whole breast with a daily fraction of 1.8 to 2 Gy; this dose fractionation is regarded to be effective and safe, considering both the excellent local control rate and the low probability of severe radiation-related toxicity (1).

Mild acute radiation dermatitis is commonly observed during or shortly after the completion of radiotherapy. However, large interindividual variations in the severity of dermatitis exist even when the patients have been uniformly irradiated. Approximately 5% to 10% of patients develop moderate to severe acute radiation dermatitis following whole-breast radiotherapy (2, 3).

Variations in the severity of radiation dermatitis are influenced by both treatment-related and patient-related

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factors. Treatment-related factors include radiotherapy variables (e.g., beam energy, radiation dose, dose fractionation, overall treatment time, heterogeneity in dose distribution, and concurrent chemotherapy). Hotspots produced by radiation dose heterogeneity often result in focally enhanced dermatitis. Patient-related factors include patient age, menopausal state, physique, and coexistent diabetes mellitus or collagen disease. In addition, several genetic syndromes such as ataxia telangiectasia (4, 5), Fanconi anemia (6, 7), and Nijmegen breakage syndrome (8, 9) have been reported to account for a small, but prominent, percentage of the hyperradiosensitive population.

In the majority of patients with moderate to severe radiation dermatitis, however, the cause of the radiosensitivity is unknown, implying the existence of undetermined intrinsic factors (10). Establishing a system for predicting patients with intrinsic radiosensitivity before subjecting them to conventional radiotherapy would be clinically useful for the individualization of radiotherapy and, consequently, for improving the treatment outcome.

The aim of the present study was to identify radiation dermatitis-related single-nucleotide polymorphisms (SNP) using peripheral lymphocytes from patients who developed radiation dermatitis after whole-breast irradiation.

Materials and Methods

Patient selection and study design. A multi-institutional, case-control study comprehensively analyzing SNPs and comparing alleles between control patients and patients who were considered to have intrinsic radiosensitivity was conducted. This study was approved by the institutional review board of each institution involved in the study. Candidate patients were selected from a pool of more than 3,000 female patients who had undergone whole-breast radiotherapy following breast-conserving surgery for the treatment of early breast cancer since June 1993 at nine institutions. The eligibility criteria were as follows: (*a*) patients who had undergone a quadrantectomy or wide excision for unilateral early breast cancer, (*b*) patients who had received traditional tangential whole-breast irradiation at a total radiation dose of 44 to 52 Gy at a daily fraction of 1.8 to 2.2 Gy over a period of less than 8 wk using a cobalt-60 source or a linear accelerator generating 4 to 6 MV X-rays, (*c*) patients whose radiation dose distribution was available, (*d*) patients who did not receive systemic chemotherapy or hormonal therapy except for oral fluorouracil or tamoxifen during the radiotherapy period, and (*e*) patients whose skin reactions were followed-up for at least 6 mo after the completion of radiotherapy.

The severity of dermatitis was graded according to the National Cancer Institute Common Toxicity Criteria. The dermatitis group in the present study was regarded to represent patients with intrinsic hypersensitivity. Clinical records, photographs of the skin before and after irradiation, and the radiation dose distribution charts were carefully reviewed to exclude confounding external factors. To exclude patients with treatment-related dermatitis, patients with focal dermatitis that could be explained by comparing the dose distribution and the dermatitis distribution to reveal focal hotspots or focal boost irradiation were strictly excluded from the present study. For example, localized dermatitis of grade ≥2 that was limited to the axilla, the submammary fold, or the nipple was regarded as indicating ineligibility for inclusion in the dermatitis group. Only patients with acute radiation dermatitis of grade ≥2 distributed evenly over the irradiated skin were regarded as having intrinsic radiosensitivity and were included in the dermatitis group.

The control group was determined by selecting patients from the pool of patients who developed grade 0 to 1 dermatitis. Patient-to-patient matching between the dermatitis group and the control group was used to ensure that the two groups would be well balanced in terms of their major characteristics and therapeutic variables. The matched factors included the patients' ages, menopausal states, use of concurrent oral fluorouracil, institution where the radiotherapy was done, radiation dose fractionation, radiation quality, and the year of radiotherapy. Two typical cases from the dermatitis group and a case from the control group are shown in Fig. 1.

Between September 2001 and September 2003, 77 patients in the dermatitis group and 79 patients in the control group were interviewed to confirm their eligibility for enrollment in the study; 15 mL of peripheral venous blood were then drawn after obtaining the patient's written informed consent.

Single-nucleotide polymorphisms. To identify polymorphisms associated with radiation dermatitis, 494 genes were selected for analysis (Table 1). These genes included DNA repair genes, apoptosis-related genes, inflammation-related genes, angiogenesis-related genes, and transporter genes. We then searched for SNPs located within or close to these genes using the JSNP database (11). A total of 3,144 SNPs were selected for genotyping. A complete list of the SNPs used in the present study is available on our Internet web page (URL to be updated).

Genotyping. After informed consent was obtained, 15 mL of peripheral blood were obtained from each patient. DNA was extracted from mononuclear cells using standard methods. Genotyping was done according to the high-throughput SNP typing method developed at Riken (12). Fluorescent signals were detected using Tecan Ultra (Tecan Group Ltd.). The genotypes were determined using automated genotyping software (13).

Statistical analysis. The associations between the SNPs and radiation dermatitis were examined using a test for independency with a 2×3 contingency table, in which the two distributions corresponded to patients with and those without radiation dermatitis. As we had already selected candidate genes that we suspected to be associated with radiation dermatitis, the SNPs were searched for in a manner that minimized the chance of missing any SNP associated with dermatitis. For this reason, the cutoff point was set at $P < 0.01$. We selected a locus when multiple SNPs mapped to that region were associated with radiation dermatitis at a P value smaller than the cutoff value. After

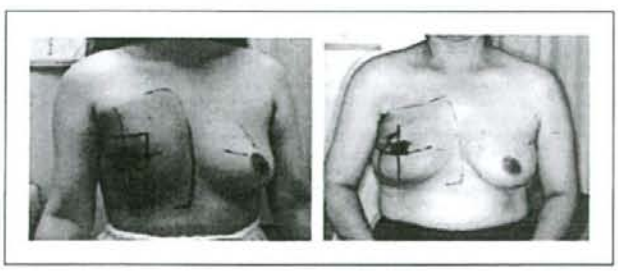

Fig. 1. Two typical cases from the dermatitis group and a case from the control group. Left, dermatitis group; right, control group.

Table 1. List of genes investigated in this study

ABCA1	*BIRC4*	*CD28*	*CYP2A6*	*FGF2*	*IL13RA2*	*MSH4*	*RAD18*	*SP1*	*TOP3B*
ABCA4	*BIRC5*	*CDA*	*CYP2A7*	*FLT1*	*IL14*	*MSH6*	*RAD23A*	*STAT1*	*TP73*
ABCA5	*BIRC6*	*CDC2*	*CYP2B6*	*FMO1*	*IL16*	*MT1H*	*RAD50*	*STAT4*	*TP73L*
ABCB1	*BIRC7*	*CDC25A*	*CYP2C18*	*FMO5*	*IL17*	*MTF1*	*RAD51*	*STAT5A*	*TRAF1*
ABCB11	*BIRC8*	*CDC25B*	*CYP2C8*	*FOS*	*IL18BP*	*MTHFR*	*RAD51L1*	*STAT6*	*TRAF5*
ABCB4	*BLM*	*CDC25C*	*CYP2C9*	*G22P1*	*IL18R1*	*MUTYH*	*RAD51L3*	*STE*	*TTRAP*
ABCC1	*BLR1*	*CDK1B*	*CYP2D6*	*GADD45A*	*IL19*	*MVP*	*RAD52*	*SULT1A2*	*TUBA1*
ABCC2	*BMPR1B*	*CDK2*	*CYP2E*	*GATA3*	*IL1A*	*MYC*	*RAD54L*	*SULT1A3*	*TUBA2*
ABCC3	*BMPR2*	*CDK3*	*CYP3A4*	*GCLC*	*IL1B*	*NAT2*	*RAD9A*	*SULT1B1*	*TUBA3*
ABCC4	*BRAP*	*CDK4*	*CYP3A5*	*GCLM*	*IL1R1*	*NBS1*	*RAF1*	*SULT1C1*	*TUBA4*
ABCC5	*BRCA1*	*CDK5*	*CYP3A7*	*GPR81*	*IL1R2*	*NDRG1*	*RASA1*	*SULT2A1*	*TUBB5*
ABCC6	*BRCA2*	*CDK6*	*CYP7A1*	*GPX2*	*IL2*	*NEIL2*	*RB1*	*SULT2B1*	*TYMS*
ABCG1	*BUB1B*	*CDK7*	*CYP7B1*	*GPX3*	*IL27w*	*NF1*	*RBL1*	*TAP2*	*UGT1*
ABCG2	*BUB3*	*CDKN1A*	*DAXX*	*GPX4*	*IL2RA*	*NFATC2*	*RBL2*	*TBP*	*UGT1A9*
ABL1	*CASP10*	*CDKN1B*	*DCK*	*GSK3B*	*IL3*	*NFATC3*	*RECQL5*	*TBX21*	*UGT2A1*
ABL2	*CASP3*	*CDKN1C*	*DCLRE1A*	*GSR*	*IL4*	*NFATC4*	*RFC1*	*TCP10*	*UGT2B15*
ADH1A	*CASP6*	*CDKN2A*	*DCLRE1B*	*GSTM1*	*IL4R*	*NFKB1*	*RPA1*	*TDG*	*UGT2B4*
ADH1B	*CASP7*	*CDKN2C*	*DCLRE1C*	*GSTM3*	*IL5RA*	*NFKB2*	*RPA2*	*TDGF1*	*UMPK*
ADH1C	*CASP8*	*CDKN2D*	*DCTD*	*GSTP1*	*IL6*	*NFKBIL1*	*RPA3*	*TEAD1*	*UMPS*
ADH4	*CASP9*	*CDKN3*	*DDB2*	*GSTT1*	*IL8RB*	*NME1*	*RRM1*	*TERF1*	*VEGF*
ADH6	*CAT*	*CER1*	*DDR1*	*H2AFX*	*IL9*	*NQO1*	*RUVBL2*	*TERT*	*VEGFB*
ADPRT	*CCBP2*	*CES1*	*DHFR*	*HAVCR2*	*IRF1*	*NQO2*	*SIRT1*	*TFDP1*	*VEGFC*
ADPRTL2	*CCL1*	*CES2*	*DMC1*	*HIF1A*	*ITGB2*	*NRP1*	*SLC10A1*	*TFDP2*	*WEE1*
ADPRTL3	*CCL11*	*CFLAR*	*DPYD*	*HM74*	*JAK1*	*NUMB*	*SLC15A1*	*TGFB1*	*WRN*
ALDH1A1	*CCL13*	*CHEK1*	*DRD2*	*HMOX1*	*JAK3*	*OAT*	*SLC15A2*	*TGFB1I1*	*WT1*
ALDH3A1	*CCL15*	*CHEK2*	*DUT*	*HMOX2*	*KDR*	*ODC1*	*SLC16A1*	*TGFB2*	*XAB2*
ALDH3A2	*CCL17*	*CHUK*	*E2F1*	*HNK-1ST*	*KIAA1821*	*PCAF*	*SLC17A4*	*TGFB3*	*XCL1*
ALDH3B1	*CCL18*	*CIP1*	*E2F2*	*HSPA1B*	*KITLG*	*PCNA*	*SLC21A11*	*TGFBI*	*XCL2*
ALDH3B2	*CCL2*	*CKN1*	*E2F3*	*HSPA2*	*LIG1*	*PDGFB*	*SLC21A12*	*TGFBR1*	*XPA*
ALDH9A1	*CCL22*	*COMT*	*E2F5*	*HSPA5*	*LIG3*	*PDGFRB*	*SLC21A3*	*TGFBR2*	*XPC*
AMHR2	*CCL24*	*CREBBP*	*EGF*	*HSPA8*	*LRDD*	*PEMT*	*SLC21A6*	*TGFBR3*	*XRCC1*
APAF1	*CCL25*	*CRYAB*	*EGFR*	*HSPA9B*	*MAD1L1*	*PGF*	*SLC21A8*	*TH1L*	*XRCC2*
ATIC	*CCL26*	*CSF1*	*EP300*	*HSPCA*	*MAD2L1*	*PIG3*	*SLC21A9*	*THBS1*	*XRCC3*
ATM	*CCL28*	*CSF3*	*EPHX1*	*HSPCB*	*MAD2L2*	*PIK3C2B*	*SLC22A1*	*THRA*	*XRCC4*
ATP1A2	*CCL3*	*CSNK1A1*	*EPHX2*	*HTFR3B*	*MAF*	*PIK3CA*	*SLC22A2*	*TIMP3*	*XRCC5*
ATP1A3	*CCL5*	*CSNK2A1*	*ERCC1*	*HTR3A*	*MAP2*	*PIK3CG*	*SLC22A3*	*TK1*	*YY1*
ATP1B1	*CCL7*	*CSNK2A2*	*ERCC2*	*HTR3B*	*MAP2K7*	*PMAIP1*	*SLC22A4*	*TK2*	*ZFPM2*
ATP1B2	*CCNA1*	*CSNK2B*	*ERCC3*	*HUS1*	*MAP4*	*PMP22*	*SLC22A5*	*TNFRSF10A*	*ZNF144*
ATP1B3	*CCNA2*	*CX3CL1*	*ERCC4*	*IFNB1*	*MAPK8*	*PMS1*	*SLC22A6*	*TNFRSF10B*	
ATP1B4	*CCND1*	*CX3CR1*	*ERCC5*	*IFNG*	*MAPK8IP2*	*PMS2*	*SLC22A7*	*TNFRSF11A*	
ATP7B	*CCND3*	*CXCL1*	*ERCC6*	*IGFBP3*	*MAPT*	*PNKP*	*SLC22A8*	*TNFRSF1A*	
ATR	*CCNE2*	*CXCL12*	*ESR1*	*IGSF6*	*MBD4*	*POR*	*SLC35A2*	*TNFRSF1B*	
ATRX	*CCNH*	*CXCL13*	*EXO1*	*IKBKB*	*MDM2*	*PPP1R15A*	*SLC38A1*	*TNFRSF6*	
BAD	*CCR1*	*CXCL14*	*FAF1*	*IL10*	*MGMT*	*PRKCA*	*SMC1L1*	*TNFRSF6B*	
BANF1	*CCR2*	*CXCL6*	*FANCA*	*IL11*	*MLH1*	*PRKCB1*	*SMC2L1*	*TNFSF10*	
BAX	*CCR5*	*CXCR3*	*FANCC*	*IL12A*	*MLH3*	*PRKCG*	*SMC4L1*	*TNFSF6*	
BCL2	*CCR6*	*CXCR4*	*FANCD2*	*IL12B*	*MNAT1*	*PRKCQ*	*SMPD2*	*TOP1*	
BID	*CCR7*	*CXCR6*	*FANCE*	*IL12RB1*	*MPG*	*PRKDC*	*SOD1*	*TOP2A*	
BIRC1	*CCR9*	*CYP17*	*FANCF*	*IL12RB2*	*MRE11A*	*PTGER2*	*SOD2*	*TOP2B*	
BIRC3	*CCRL1*	*CYP1B1*	*FANCG*	*IL13*	*MSH2*	*RAD17*	*SOD3*	*TOP3A*	

screening the loci, a Fisher's exact text for a 2 × 2 contingency table was done on all possible SNPs mapped to and around the loci, assuming allele frequency, dominant, or recessive models.

Estimation of probability of radiation dermatitis. The probability of radiation dermatitis was calculated for each combination of the two SNPs selected during the second-step screening process. To compute the probability, a logistic regression model with four indicator variables for the two different SNPs was adopted. The allele frequencies of each genotype combination were then calculated based on the allele frequency of individual SNPs obtained from our genotyping data of 1,594 unrelated Japanese individuals.

Results

Patient characteristics. The major patient characteristics and therapeutic variables are summarized in Table 2. About the patient-related factors, age, menopausal state, and the pathologic T and N classifications were similar in the radiation dermatitis and control groups. The two groups were generally well balanced with regard to the treatment-related factors such as the type of surgery, period between surgery and the commencement of radiotherapy, the presence of concurrent chemotherapy with oral fluorouracil, the radiation source, the total radiation dose to the whole breast, the dose per fraction, the overall treatment time for whole-breast radiation, and the accumulative dose per week. A significant difference was found for only one factor, the presence of concurrent tamoxifen chemotherapy; 51% of the radiation dermatitis group and 68% of the control group ($P = 0.024$) had received tamoxifen during the radiotherapy period.

Genotyping of SNPs. The genotypes of several loci were determined using an Invader assay in 156 patients with breast